

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Bucolo et al.
Application No.	:	10/812,551
Filed	:	March 29, 2004
Title	:	NEW FREE-RADICAL SCAVENGER CONTAINING VISCOELASTIC COMPOSITION, METHODS OF USE AND PACKAGE
Examiner		Benjamin J. Packard
Group/Art Unit	:	1612
Conf. No.	:	3392
Docket No.	:	P03491

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Sir:

In response to the Notification of Non-Compliant Appeal Brief dated May 11, 2009, Applicants submit a revised Appeal Brief under 37 C.F.R. § 41.37. As the requisite fee under 37 C.F.R. § 41.20(b)(2) was submitted in the initial filing no fee is due. Because the initially submitted brief did not include sub-headings in the argument section that match the grounds for rejection, the appeal brief is submitted in whole minus the requisite appendices.

TABLE OF CONTENTS

REAL PARTY IN INTEREST	3
RELATED APPEALS AND INTERFERENCES	3
STATUS OF CLAIMS	3
STATUS OF AMENDMENTS	3
SUMMARY OF CLAIMED SUBJECT MATTER	3 - 4
GROUND OF REJECTION	4
ARGUMENT	
1. Introduction	5 – 7
2. Examiner’s Position	7 – 9
3. Summary of Cited Art	9 – 11
4. Discussion and Applicants’ Position	11 - 20
Claims 1, 6, 8-10, 20 and 25-28	15 – 17
Claim 7	18
Claim 11	18 – 19
Claim 47	19
Claim 22	20
APPENDICES	
Claims	
Evidence	
Related proceedings	

REAL PARTY IN INTEREST

The real party in interest is Bausch & Lomb, Inc. having its principal place of business at One Bausch & Lomb Place, Rochester, NY.

RELATED APPEALS AND INTERFERENCES

None

STATUS OF CLAIMS

The claims subject to this Appeal are claims 1, 6-11, 20, 22, 25-28 and 47 all of which are under final rejection. Claims 2-5, 12-14, 18, 19, 21, 23, 24, and 29-46 are canceled. Claims 15-17 are withdrawn. No claims have been allowed. A listing of the claims subject to this Appeal are provided in the requisite Appendix.

STATUS OF AMENDMENTS

The claim amendments presented in the Amendment and Response under 37 C.F.R. § 1.111, filed November 4, 2008 were entered by the examiner.

SUMMARY OF CLAIMED SUBJECT MATTER

With respect to claim 1, the claimed subject matter is directed to a viscoelastic composition comprising a viscoelastic polymer. The viscoelastic polymer comprises a mixture of hyaluronic acid and/or salts thereof and hydroxypropyl methylcellulose. See, title and page 1, 1st paragraph; page 3, 2nd paragraph. The concentration of hyaluronic acid and/or salts thereof is a minimum of about 0.1%w/v and a maximum of about 6%w/v and the concentration of hydroxypropyl methylcellulose is a minimum of about 0.05%w/v and a maximum of about 5%w/v, based upon the total volume of the viscoelastic composition. Page 3, 2nd paragraph; original claim 1. The composition also comprises tris[hydroxymethyl]aminomethane at a maximum of about 50mM and a

minimum of about 0.1mM based upon the total weight of the viscoelastic composition.

Id. The composition also comprises a hexahydric alcohol. Id.

With respect to claim 42, and as in claim 1, the claimed subject matter is directed to a viscoelastic composition comprising a viscoelastic polymer. The viscoelastic polymer comprises a mixture of hyaluronic acid and/or salts thereof and hydroxypropyl methylcellulose. See, title and page 1, 1st paragraph; page 3, 2nd paragraph. The concentration of hyaluronic acid and/or salts thereof is a minimum of about 0.1%w/v and a maximum of about 6%w/v and the concentration of hydroxypropyl methylcellulose is a minimum of about 0.05%w/v and a maximum of about 5%w/v, based upon the total volume of the viscoelastic composition. Page 3, 2nd paragraph; original claim 1. The composition also comprises tris[hydroxymethyl]aminomethane at a maximum of about 50mM and a minimum of about 0.1mM based upon the total weight of the viscoelastic composition. Id. The composition also comprises a hexahydric alcohol. Id. the hexahydric alcohol is selected from mannitol or sorbitol. Page 5, 3rd, paragraph; original claims 2 and 3. Also, the viscoelastic composition possesses an optimal viscosity profile having a zero-shear viscosity from $6 \cdot 10^4$ cps to $4 \cdot 10^6$ cps, and a high-shear viscosity from 500 cps to 2000 cps. Page 9, 2nd and 3rd paragraphs; original claims 13 and 14.

GROUND OF REJECTION

Whether claims 1, 6-11, 25-28 and 47 are obvious under 35 U.S.C. § 103(a) over Singh et al. (US 2003/0232089) in view of Olejnik et al. (US 5,597,559) and Gohzu et al. (US 5,013,445).

Whether claim 20 is obvious under 35 U.S.C. § 103(a) over Singh in view of Olejnik and Gohzu, and further in view of Cantoro (US 5,597,599).

Whether claim 22 is obvious under 35 U.S.C. § 103(a) over Singh in view of Olejnk and Gohzu, and further in view of Katz (US 4,287,175).

ARGUMENT

I. Whether claims 1, 6-11, 25-28 and 47 are obvious under 35 U.S.C. § 103(a) over Singh et al. (US 2003/0232089) in view of Olejnk et al. (US 5,597,559) and Gohzu et al. (US 5,0134,45), and whether claim 20 is obvious under 35 U.S.C. § 103(a) further in view of Cantoro (US 5,597,599).

1. Introduction.

The natural crystalline lens of the eye plays a primary role in focusing light onto the retina for proper vision. With aging, however, cloudy spots slowly develop, which cause one's vision to blur. We refer to these cloudy spots as cataracts. In fact, more than forty percent of persons aged 75 to 85 will develop cataracts in one or both eyes. To restore vision, the natural lens is replaced with an intraocular lens (IOL).

The surgical procedure begins with removing the natural lens through a small incision in the lens capsule –a membrane that contains the natural lens. The small incision procedure provides quick response healing and greater vision acuity following surgery. A sonification probe is inserted through the incision to emulsify the cataractous lens. The emulsified fragments of the lens are then removed (aspirated) and flushed from the eye (lens capsule). An IOL, typically in a folded state is inserted through the incision and into the empty lens capsule. Once the IOL is inserted into the lens capsule, the lens is carefully unfolded and properly positioned by the surgeon.

To protect the surrounding ocular tissues from trauma or injury during the cataract surgical procedure, e.g., through inadvertent contact with surgical instruments or due to the disruption of the normal ocular environment, viscoelastic compositions are used to

coat and cushion the surrounding ocular tissues. Application, pages 1 (bottom) - 2 (top). Viscoelastic compositions have a unique viscosity profile such that under high shear, e.g., when forcing the composition through a syringe needle, the composition has a relatively low viscosity, whereas under low or static shear, e.g., when occupying an ocular volume within the eye, the compositions have relatively high viscosity. Accordingly, the viscoelastic can be easily inserted and aspirated (removed) from the eye, but after placement in the eye the compositions form a stable cushion that protects the tissues during surgery.

In addition, viscoelastic compositions can be classified based on their particular viscoelastic properties. A “dispersive” viscoelastic will have a syrupy consistency similar to honey, whereas a “cohesive” viscoelastic will behave more like a solid than liquid and have a consistency similar to jam or gelatin. The dispersive class is great for coating the cornea and protecting the corneal endothelium from ultrasound-induced phaco trauma and the fluid currents used during cataract (lens) removal. However, because the dispersive class of viscoelastic compositions spread and coat so well they are more difficult to remove at the end of the surgical procedure. The cohesive class of viscoelastic compositions is best at creating and maintaining space or volume, and displacing or stabilizing ocular tissues. Also, the highly cohesive nature of the compositions provides for relatively easy removal by aspiration. The commercial market has attempted to take advantage of these differences in viscoelastic properties by offering surgical kits that contain both dispersive and cohesive viscoelastics.¹ This approach,

¹ Dual-viscoelastic systems are available from Advanced Medical Optics as the duo-OVD named Healon D+GV, which consists of Healon D (dispersive) and Healon GV (greater viscosity cohesive), and from Alcon Laboratories as Duovisc, which consists of Provisc (cohesive) and Viscoat (dispersive). In addition,

however, does not necessarily provide an optimal, single viscoelastic composition for surgical use. The inventive compositions were developed such that their viscoelastic properties behave neither like a dispersive or a cohesive, and instead, possess their own particular viscosity profile. With this background in the art we address the rejections at hand.

2. Examiner's Position.

The examiner's rejection of the claims under § 103(a) is summarized as follows. The Examiner notes that the prior art collectively discloses each of the various components of the claimed compositions specifically based on function. Advisory Action, 2nd paragraph. "Where the substitution of components based on their known function would be obvious to one of ordinary skill in the art, the focus then appears to be on the motivation for this specific combination." *Id.* Moreover, "[w]here the various groups of compounds are disclosed as substitutable and *appear to be well known equivalents for the same purpose*, the substitution of the various components would be well within the level ... skill in the art to make such substitutions." *Id.* (emphasis added)

[I]t would be obvious to one of ordinary skill in that [*sic*, the art] to substitute the disclosed "gum" compounds, such as hyaluronic acid for Scleroglucan in the working example ID 21 [disclosed in Singh]. The addition of the tonicity adjusting agent of Olejnik would be obvious where the addition of such an additional component was taught. Further where the addition of buffering agents is disclosed, and the amount would be a matter of routine optimization based on the desire to achieve a physiological pH similar to disclosed in Gohzu et al.

With regard to the viscosity, percentage of quenching and shear-viscosities, [in reference to claims 26 and 27] these appear to be conventional in the art, such that their determination would have been

separate tubes of viscoelastics from other manufacturers can be used, such as using Bausch & Lomb Amvisc (cohesive) and Ocucoat (dispersive).

obvious to one of ordinary skill in the art using no more than routine experimentation.”

Non-final Official Action, October 15, 2008, page 4.

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness. Essentially, the Examiner starts with Example ID 21 of Singh and then begins to make individual component substitutions to the Example using the Applicants claimed composition as a blueprint. The Examiner then adopts the position that such substitutions would be obvious to one of ordinary skill under § 103(a) and the guidance of the Court in *KSR International v. Teleflex*, 127 S.Ct. 1727 (2007). Applicants respectfully submit that the Examiner has committed legal error based on the knowledge described in the cited references in their entirety, and the alleged motivation that is said to spring forth from that art or from the general knowledge of one of ordinary skill to make the component substitutions the Examiner proposes.

The Examiner’s proposed combination is purely conclusory, and the rejection fails to explain why one of ordinary skill would look to the cited art, and in particular, to the secondary references, to cure the stated deficiencies in Singh. The rejection fails to provide an evidentiary basis, or a finding of fact, to support the Examiner’s picking and choosing of previous known components used in ophthalmic compositions. For example, following a careful review of the art in its entirety, why would one of ordinary skill substitute hyaluronic acid for scleroglucan in Singh’s ID21 as proposed? There must be at least one hundred different natural and synthetic polymers with the known capability of functioning as a viscosity modifier from which one of ordinary

skill in the art can choose from. Greater evidence is required, and not simply that either is considered a biopolymer or is referred to in the art as a viscosity modifier.

3. The Cited Art.

Two of the three cited references, Singh and Olejnik, describe eye drop compositions, and the third, i.e., Gohzu et al., describes a solid-phase gel used to separate very large proteins, specifically of the immunoglobulin G subclass, by liquid chromatography. A buffer solution is used as the mobile phase and can include one of five buffer types with phosphate and TRIS being preferred.

Singh describes an ophthalmic composition that includes a pharmacologically active agent and a mixture of at least two gum polymers. The mixture of the gum polymers is said to increase the retention time of the active agent in the eye. See, Abstract. As Singh describes, a major problem with the administration of ophthalmic drugs is the “rapid and extensive precorneal loss caused by drainage and high tear fluid turnover.” In other words, how can one of ordinary skill develop an eye drop formulation that allows the active agent to remain in the eye for a time sufficient to therapeutically treat a particular ocular condition? We are all familiar with placing an eye drop solution in the eye and experiencing the wash out affect caused by an immediate tear flow response.

To address this problem, those in the art looked to increase the viscosity of the formulations hoping that the more viscous the formulation, the more difficult it would be for the formulation to wash out. Singh describes the use of various combinations of gelling agents including gums. See, paragraphs [0008] to [0010]. Singh looked to improve upon the use of gelling agents to provide more effective ophthalmic

formulations by testing various combinations. In fact, Singh lists five (5) synthetic gums, sixteen (16) natural polysaccharide gums and two (2) derivatized natural polysaccharides for a total of twenty-three (23) different gums. See, paragraph [0025]. Singh also refers to the optional addition of an “ophthalmically acceptable mucoadhesive polymer” in which hydroxypropyl methylcellulose (HPMC) is one of ten (10) listed. Accordingly, the possible number of different gum or gelling agent pairings suggested in Singh is 23×10 or 230 pairings.

Olejnik describes preservative-free ophthalmic compositions, that is, eye drop formulations, used to treat various ocular conditions such as dry eye. These compositions contain a cellulosic polymer such as hydroxypropyl methylcellulose and polyalkylene glycols. Abstract, col. 2, lines 16-41. Consistent with the teachings and suggestion of Singh, the “[h]ydroxypropyl methylcellulose is employed as a thickening agent to keep the liquid in contact with the eye surface for as long as possible.” Col. 3, lines 36-38. The compositions also include agents to adjust the tonicity of the composition.² As stated, a non-ionic tonicity agent is preferred and includes sugars and sugar alcohols such as mannitol and sorbitol.

Gohzu describes a method for separating very large proteins such as immunoglobulin G (IgG) subclasses by liquid chromatography using a solid phase porous gel. The IgG proteins are separated on the column by the distinct interaction between the

² Tonicity refers to the response of cells or tissues to a particular solution. If cells are contacted with a hypertonic solution, net movement of water will be out of the cell, causing the cell to shrivel. If cells are contacted with a hypotonic solution, net movement of water will be into the cell, causing the cell to swell or burst. In the case of eye drops, the tonicity of the formulation is adjusted with respect to ocular tissues and cells such that there is little net movement of water across cell membranes. Accordingly, an ophthalmic solution is adjusted within a set osmolarity range (measured in milliosmols) so that it will have the desired tonicity with respect to ocular cells or tissues.

solid support gel and the hydrophobic content of the individual proteins. Col. 1, line 64 to col. 2, line 2. Buffer solutions are used as the mobile phase for the proteins as they progress along the column. The buffer solutions include known biological buffer systems such as borate, phosphate and tris[hydroxymethyl]aminomethane (TRIS).

Applicants are not exactly sure why the Examiner cites to the secondary references as each of the chemical components recited in the claims at issue can be found in Singh alone. For example, Singh also describes the optional addition of an osmolality agent including the typical metal and organic salts as well as sugars including mannitol. A total of about twelve agents are listed only one of which is a hexahydric alcohol. Also, Singh prefers to use ionic salts over the sugar types. Paragraph [0093]. Yet, the examiner proposes a combination with a sugar alcohol – why? Singh also refers to the optional addition of a buffering agent. Paragraph [0094]. Singh lists thirteen (13) buffer components with no particular preference, one of which is TRIS. Accordingly, the possible number of combinations described in Singh is $23 \times 10 \times 13 \times 12$ or 35,880 compositions, i.e., nearly 36,000 possible combinations – all of which are reasoned and concluded by the examiner to be *prima facie* obvious to one of ordinary skill. Applicants ask what led the Examiner down the path to pick the one combination out of a possible 36,000. Could it be the Applicants' own teaching?

4. Discussion and Applicants' Positions

In support of the rejection, the examiner relies on select statements of the Court in *KSR*, 127 S.Ct. 1727, *supra*, however, *KSR* is not the lens through which an obviousness analysis under §103 is to be conducted. Rather, a proper § 103 analysis is still governed by *Graham v. John Deere Co. of Kansas City*, 338 U.S. 1 (1966). Following a review of

the content of the prior art as a whole and the scope of the patent claim, the differences between the prior art and the claims at issue are to be ascertained with the knowledge and understanding of one of ordinary skill in the art. *KSR*, 127 S.Ct. at 1734.

The Examiner's reliance on the statement regarding the "simple [arrangement of] old elements" to support the rejection of all claims is not the Court's holding in *KSR*. In fact, the statement relied upon arose from a "broadbrush" understanding and conclusion of another case, *Sakaraida v. AG Pro Inc.*, 425 U.S. 273, 282 (1976).³ Nevertheless, the Examiner relies upon the statement as if it was a bright-line rule for invalidating "combination" claims of novel chemical compositions. Again, *KSR* does not establish a new or alternative framework for applying the statutory language of § 103. The framework to be applied remains that of *Graham*. The Court's reasoning in *KSR* is best summarized as follows, and not by select statements taken out of context.

Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the market place; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ... See *In re Kahn*, 441 F. 3d 977, 988 (CA Fed. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

³ In *Sakaraida*, the Court asks whether the improvement is more than the predictable use of prior art elements according to their established functions.

KSR, 127 S.Ct. at 1740-41. The *KSR* Court reaffirms *Graham* and rejects the rigid application of the ‘teaching, suggestion, or motivation test (TSM test)’.⁴

After reminding us of the flexible approach to decide the question of obviousness, the Court provides additional comments on combination patents. Notably, the Court rejects the rigid approach taken by the Examiner that all combination patents are *prima facie* obviousness. In talking directly to the examination core, the Court states

a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, *it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does*. This is so because inventions, in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some cases, is already known.

Id. at 1741. (emphasis added)

The rejection of all claims is based upon an incorrect understanding of the Supreme Court’s holding in *KSR*, and particularly how that holding is to be applied to the chemical arts. Inconsistent with *KSR*, the rejection puts forth a rigid, bright-line rule that “when a patent simply arranges old elements with each performing the same function it

⁴ In *KSR*, the Federal Circuit committed at least two errors; first, they failed to properly account for the nature of the problem to be solved and the common sense approach one of ordinary skill would take to solve that problem, and second, they failed to give sufficient weight to a reference that was not of record during prosecution. In both instances, the errors resulted from their rigid application of the TSM test. Particularly, in the later instance, the Federal Circuit erred because they required the prior art references to specifically address the precise problem that the patentee was trying to solve. 127 S.Ct. at 1737-38. The Court disagreed. “Throughout this Court’s engagement with the question of obviousness, our cases have set forth an expansive and flexible approach inconsistent with the way the Court of Appeals applied its TSM test here.” *Id.* at 1739 “The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents [or published patent applications].” *Id.* at 1741

had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious.” By adopting such a rule the Examiner commits legal error. Specifically, no reason is provided by the Examiner as to why one of ordinary skill could combine the four essential components to form the claimed viscoelastic compositions. The Examiner merely states that “it would have been obvious to have selected various gums from within a prior art disclosure [Singh], to arrive [at, *sic*] compositions ‘yielding no more than one would expect from such an arrangement’”. Final Rejection, 01/2009, page 3. Moreover, “[w]ith regard to the viscosity, percentage of quenching [claim 11], and shear-viscosities [claims 26, 27 and 47], these appear to be conventional in the art, such that their determination would have been obvious to one of ordinary skill in the art using no more than routine experimentation.” Non-final Rejection, 10/2008, page 4. Essentially, the Examiner presents the Board with a rigid rule that all compositions comprising a combination of previously known components is *prima facie* obvious under § 103. Applicants vehemently reject that rule and respectfully submit that the holding of *KSR* does not extend to the point the Examiner wishes to take us.

Applicants specifically request the Board of Patent Appeals and Interferences to consider the following grouping of claims.

Group A	1, 6, 8-10, 20 and 25-28
Group B	7
Group C	11
Group E	47
Group F	22

Group A: Claims 1, 6, 8-10, 20 and 25 - 28

The invention of claims 1, 6, 8-10, 20 and 25 - 28 is directed to a viscoelastic composition comprising two different viscoelastic polymers – hyaluronic acid and hydroxypropyl methylcellulose (HPMC). The term “viscoelastic” is recited in the claims and the preamble. Therefore, there should be no question that the invention claimed must exhibit a viscosity profile recognized by one of ordinary skill in the art as a viscoelastic composition. It is well established that a compound or a composition and its properties are inseparable. *In re Papesch*, 315 F.2d 381 (C.C.P.A. 1963). The person of ordinary skill may be a chemist with several years of developing viscoelastic compositions or a surgeon with several years of training on the use of a viscoelastic composition during surgery. It is through the eyes of these persons of skill in which the invention needs to be viewed. Accordingly, a stated rejection under § 103(a) must carefully consider who the person of ordinary skill is and armed with the art as a whole and with some understanding of his or her general knowledge in the area provide evidentiary support and sufficient reasons why that person would combine the four recited chemical components to arrive at Applicants’ claimed viscoelastic compositions.

The Examiner relies upon Singh for the selection of hyaluronic acid from a list of twenty-three gums and for the selection of HPMC from a list of ten “acceptable mucoadhesive polymer”. There exists no particular preference for hyaluronic acid or for the addition of the optional mucoadhesive polymer. The possible combinations, even assuming one was to add an optional mucoadhesive polymer, are 23×10 or 230 different combinations, all of which are reasoned and legally concluded by the Examiner to be obvious to the person of ordinary skill. Applicants respectfully submit that the relatively

large number of possible combinations alone is sufficient to defeat the Examiner's alleged *prima facie* case.

Upon a closer review, Singh directs one of ordinary skill to use a combination of gums to produce "unexpected advantages over individual gums". Paragraphs [0041] and [0044-53]. To optimize these unexpected advantages one of skill is directed to use a nonionic gum in combination with an anionic gum. For example, scleroglucan is listed as a neutral gum and hyaluronic acid is listed as an anionic gum. Given this more careful reading of Singh one of ordinary skill would rather add hyaluronic acid to ID21 rather than substitute the hyaluronic acid for the scleroglucan as proposed. Moreover, Singh's anionic gum of choice is propylene glycol alginate or alginic acid, not hyaluronic acid. In fact, six of the ten preferred gum combinations include propylene glycol alginate or alginic acid. See, Paragraphs [0044-53]. Therefore, one of ordinary skill having read Singh in its entirety would very likely choose alginic acid or one of its derivatives to combine with scleroglucan, and not as examiner proposes to substitute hyaluronic acid for scleroglucan.

In addition, scleroglucan is a nonionic branched homopolysaccharide that gives only D-glucose upon complete hydrolysis, and every third unit bears a branched β -D-glucopyranosyl unit. Scleroglucan is produced by fungi, and is not found in mammalian tissues. Hyaluronic acid is an anionic glycosaminoglycan, and is best described as a polymer disaccharide composed of D-glucuronic acid and D-N-acetylglucosamine. Hyaluronic acid is found throughout mammalian connective, epithelial and neural tissues. For example, hyaluronic acid is a major component of synovial "joint" fluid. Yet, in spite of the differences in chemical structure and biological function of these two natural

compounds, the Examiner, without reliance on any scientific or technical evidence, proposes that one of ordinary skill in the art would find it obvious to substitute hyaluronic acid for scleroglucan in Singh's Example ID 21 given the direction of the art, and in particular Singh, in its entirety. Moreover, such a proposal under § 103 necessarily assumes that such a substitution would provide a viscosity profile required of a viscoelastic composition. Applicant respectfully disagrees with the Examiner's legal conclusion and submits that on this point alone the Examiner's assertion of a *prima facie* case of obviousness falls.

The claims at issue require, however, that we continue the "picking and choosing" to the selection of tris[hydroxymethyl]aminomethane (TRIS) and then to a nonionic osmolality agent, i.e., a hexahydric alcohol. As stated earlier, based upon the description of Singh alone, the potential number of combinations is $23 \times 10 \times 13 \times 12$ or 35,880 compositions – all of which are reasoned and concluded by the Examiner to be *prima facie* obvious to one of ordinary skill.

Applicants must ask why one of ordinary skill having the cited references in hand, and having the knowledge of a chemist or a surgeon familiar with developing or using viscoelastic compositions, pick and choose the claimed compositions of claims 1, 6, 8-10, 20 and 25 - 28 out of a possible 36,000? We are reminded that we are not referring to a mechanical gas pedal having a fixed or an adjustable pivot point, i.e., a 50:50 selection, as in *KSR*. Unless this question is answered through reliance upon sufficient evidence and sound reasoning, a proper case of *prima facie* obviousness has not been presented. Applicants respectfully request that the rejection of claims 1, 6, 8-10, 20 and 25 - 28 be withdrawn.

Group B: Claim 7

Claim 7 is directed to a viscoelastic composition that comprises hyaluronic acid, HPMC and TRIS, all within their respective concentration ranges, and sorbitol. Olejnik, like Singh, describes an eye drop formulation, one difference being that Olejnik looks to the use of non-ionic tonicity agents such as sugar alcohols to provide an appropriate osmolality value to the formulation. Applicants wonder if Singh is said to prefer ionic osmolality agents why would one of ordinary skill look to a reference that prefers non-ionic agents. Also, given that one of ordinary skill would possess the knowledge that a widely accepted hyaluronic acid-based viscoelastic presently on the market, Healon, utilizes sodium chloride as an osmolality agent, and phosphate buffer (see, attached product description in Evidence Appendix), again why would one of skill be directed to the claimed viscoelastic compositions. Applicants respectfully ask why one of ordinary skill would be motivated to diverge from a sodium chloride, phosphate buffer preferred in Singh and a long-standing, commercial product and find it obvious to substitute TRIS/sorbitol?

The answer to the last question is quite clear. Applicants submit that the path the Examiner takes to the selection of a sugar alcohol over an ionic agent, and the selection of TRIS over other biological buffer components is the path of hindsight, which we know to be improper. Applicants respectfully request that the rejection of claim 7 be withdrawn.

Group C: Claim 11

An important property of any marketable viscoelastic composition is the long-term stability or shelf-life of the composition. With respect to viscoelastic compositions,

particularly, viscoelastic compositions that contain hyaluronic acid, some degradation of the hyaluronic acid, and hence, a change in the viscosity profile of the composition is expected. Applicants were confronted with the problem of stabilizing the claimed compositions. The addition of the TRIS/sorbitol enhances the stability (shelf-life) of the claimed compositions.

Each of the formulations containing tris[hydroxymethyl]aminomethane and/or sorbitol had higher free radical quenching than samples without either. Tris[hydroxymethyl]aminomethane and sorbitol individually have free-radical quenching properties. The combination of tris[hydroxymethyl]aminomethane and sorbitol have the best free-radical quenching properties.

Application page 17, bottom. The quenching profile recited in claim 11 recognizes the unique, long-term stability properties of the claimed compositions. Applicants respectfully request that the rejection of claim 11 be withdrawn.

Group E: Claim 42

Claim 42 further defines the viscoelastic compositions of claim 1 by further reciting the hexahydric alcohol as sorbitol or mannitol, and the viscosity profile of claims 26 and 27. Applicants submit that claim 42 is nonobvious for the same reasons claims 1, 26 and 27 are nonobvious. The teachings and suggestions of the cited references fails to direct one of ordinary skill in the art with sufficient specificity such that one would select that one composition from the 36,000 possible combinations described in Singh, and arrive at a viscoelastic composition having the recited viscosity parameters. Accordingly, Applicants respectfully request that the rejection of claim 42 be withdrawn.

II. Whether claim 22 is obvious under 35 U.S.C. § 103(a) over Singh in view of Olejnik and Gohzu, and further in view of Katz (US 4,287,175).

Group F: Claim 22

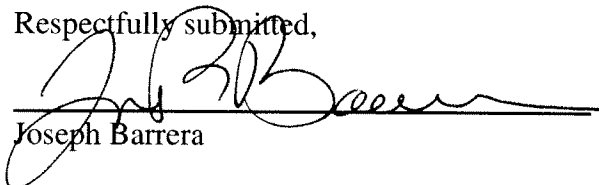
Commercial sources of pharmaceutical grade HPMC are typically characterized as either a low molecular weight form or high molecular weight form. Applicants specifically selected the low molecular weight form to include in the claimed compositions.

The average molecular weight of the hydroxypropylmethylcellulose is a minimum of about 10 kD and a maximum of about 120 kD according to one embodiment. Typically, the average molecular weight of the hydroxypropylmethylcellulose is minimum of about 10 kD, about 12 kD or about 20 kD and a maximum of about 120 kD, about 90 kD or about 86 kD.

Application, page 8 (bottom) to page 9 (top). There is no guidance in Singh with regard to a selection of which grade of HPMC one should use, i.e., the low molecular weight form or the high molecular weight form. Olejnik does, however, list HPMC 90HG 4000 (see, Ex. 1, col. 5), which has a reported weight average molecular weight of 89 kD. Applicants respectively request that the rejection of claim 22 be withdrawn.

Reconsideration of this application is respectfully requested for the reasons stated.

Respectfully submitted,



Joseph Barrera

Bausch & Lomb Incorporated
One Bausch & Lomb Place
Rochester, NY 14604
Tel: (585) 338-8180
Fax: (585) 338-8706
Email: joseph_barrera@bausch.com

Dated: May 19, 2009